

LETTER TO THE EDITOR | OBSTETRICS & GYNECOLOGY

Nomogram for Predicting Methotrexate Failure in Tubal Ectopic Pregnancy: Time for Prospective Validation

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To the Editor,

A tubal ectopic pregnancy occurs when a fertilized egg implants in the fallopian tube, leading to risks such as rupture, haemorrhage, and maternal morbidity. Prompt diagnosis is critical to prevent complications and protect fertility. Management options include expectant management, surgical intervention, and medical therapy. Methotrexate (MTX) is a folic acid antagonist commonly administered for stable, unruptured ectopic pregnancies because it inhibits trophoblastic growth and may avoid the need for surgery. Its effectiveness is determined by factors including initial β -hCG levels and the size of the ectopic pregnancy [1].

Numerous factors contributing to MTX failure in tubal ectopic pregnancies have been outlined in recent studies, including elevated initial serum β -human chorionic gonadotropin (β -hCG) levels, the presence of fetal cardiac activity, adnexal masses, yolk sac visibility, and free fluid observed on ultrasound. Studies evaluating early predictors of single-dose MTX failure have shown that higher Day 1 β -hCG levels, fetal cardiac activity, adnexal masses, and yolk sac presence significantly increase the likelihood of treatment failure, alongside other clinical factors such as a history of pelvic inflammatory disease and β -hCG dynamics [2]. Fu et al. identified elevated pretreatment β -hCG levels and gravidity as independent predictors and created a nomogram incorporating various risk factors, illustrating that the combination of predictors can improve individualized risk assessment [3].

A predictive nomogram that synthesizes multiple pretreatment variables, such as β -hCG levels and trends, ultrasound indicators (yolk sac, mass size, or fetal cardiac activity), gravidity, and a history of prior ectopic pregnancy, provides a useful bedside visual tool for individualized risk assessment. By consolidating these predictors into a single model, clinicians can assess the probability of methotrexate failure for each patient rather than depending on individual factors in isolation. Nomograms have been used in oncology and other fields to translate multivariable regression models into accessible instruments that facilitate shared decision-making, improve patient counselling, and enhance clinical confidence [4]. In the case of tubal ectopic pregnancy, such a nomogram could enable the early identification of patients unlikely to respond to MTX, facilitating timely surgical intervention while safely supporting medical management for those with a high likelihood of success, which has been reported to exceed 85%.

Existing predictive models for methotrexate failure in tubal ectopic pregnancy are largely constructed from retrospective data, which can result in selection bias, missing data, and potential overfitting, ultimately affecting their reliability. There is considerable variability in methotrexate treatment protocols, monitoring schedules, and definitions of failure, such as the threshold for β -hCG rise across various studies, which lessens their comparability. Furthermore, many models have not been prospectively validated or evaluated within multicenter, diverse populations, including those undergoing assisted reproductive techniques such as in vitro fertilization (IVF), where the dynamics of ectopic pregnancies may differ. Additionally, the small sample sizes in numerous studies restrict statistical power, and some critical predictors may not have been consistently accounted for [5].

Nomogram-guided methotrexate therapy enables individualized prediction of treatment failure in tubal ectopic pregnancies. It integrates a range of predictors, such as β -hCG levels, ultrasound findings, gravidity, and a history of ectopic pregnancy. By synthesizing these factors, clinicians can promptly identify patients who are unlikely to respond to MTX. This strategy supports timely surgical intervention for those at high risk while facilitating safe medical management for patients who are likely to respond successfully to MTX. Existing models are constrained by retrospective data, varying protocols, and limited sample sizes. They lack prospective, multicenter validation, especially in the context of IVF and diverse populations. Prospective research is critically needed before broad clinical adoption can occur.

References

1. Solangon SA, Van Wely M, Van Mello N, Mol BW, Ross JA, Jurkovic D. Methotrexate vs expectant management for treatment of tubal ectopic pregnancy: An individual participant data meta-analysis. *Acta Obstet Gynecol Scand*. 2023 Sep;102(9):1159–1175. doi: 10.1111/aogs.14617. Epub 2023 Jun 22. PMID: 37345445; PMCID: PMC10407021.
2. Tang L, Nie S, Ling L, Zhu Q. Predictors of treatment failure of tubal pregnancy with single-dose methotrexate regimen: a systematic review and meta-analysis. *J Obstet Gynaecol*. 2025;45(1):2447997. doi: 10.1080/01443615.2024.2447997. Epub 2025 Jan 7. PMID: 39773144.
3. Fu L, Liu X, Tian Z, Du Z, Wang X, Wang X, Li X, Xu T, Sun Z. Risk factors for methotrexate treatment failure in tubal ectopic pregnancy: a retrospective cohort study. *BMC Pregnancy Childbirth*. 2024;24(1):884. doi: 10.1186/s12884-024-07122-6. PMID: 39736575; PMCID: PMC11686986.
4. Zeevi G, Bercovich O, Haring Y, Nahum S, Romano A, Houri O, Yeoshoua E, Eitan R, Peled Y, Krissi H. Nomogram to predict methotrexate treatment success in ectopic pregnancy. *Int J Gynaecol Obstet*. 2025;168(2):620–627. doi: 10.1002/ijgo.15927. Epub 2024 Sep 26. PMID: 39324483.
5. Chen S, Zhu F, Zhang Y, Li J, Gao J, Deng G. A model to predict treatment failure of single-dose methotrexate in patients with tubal pregnancy. *Med Sci Monit*. 2020;26:e920079. doi: 10.12659/MSM.920079. PMID: 32383438; PMCID: PMC7236588.

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